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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 10/757,832	Examiner: CHEN, STACY BROWN
Applicant: Herbert W. Virgin IV	Group Art Unit: 1648
Filed: January 14, 2004	Confirmation No.: 5585
Docket No.: 60005161-0168	

Director for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION TO MAKE SPECIAL

To the Director:

Applicant hereby submits a Petition to Make Special pursuant to 37 C.F.R. § 1.102 because of actual infringement of the claims.

In accordance with the procedure for filing a PTMS set forth in MPEP § 708.02 part II, the undersigned attorney asserts:

(A) that there are infringing devices or products on the market and methods of use.

(B) that a rigid comparison of the infringing devices, methods and products with the claims of the application has been made, and that, in the undersigned attorney's opinion, some of the claims are unquestionably infringed; and

(C) that the undersigned attorney has made or caused to be made a careful and thorough search of the prior art or has a good knowledge of the pertinent art.

A rigid comparison of laboratory testing for MNV infection offered by Research Animal Diagnostic Laboratory ("RADIL") with the claims of the present application has led the undersigned attorney to the opinion that RADIL infringes several claims of the present application by making, using, selling and/or offering for sale the claimed invention. Under 35 USC § 271(a), it is an act of infringement to make, use, offer to sell, or sell any patented invention within the United States. In the present application, the claims set forth in a

Preliminary Amendment recite methods and articles for testing mice for norovirus (MNV) infection. However, RADIL advertises on an internet Web page (http://www.radil.missouri.edu/info/MNVinfo.asp) that it is offering testing of mice for MNV infection by methods claimed at least in claims 36 and 60. The Web page, in fact, cites one of Applicant's own publications on the virus. In addition, on a separate web page (http://www.radil.missouri.edu/info/MFIFAQ.pdf) RADIL discloses that they are using an assay surface that is, in the opinion of the undersigned attorney, the assay surface of claim 46. In addition, in the opinion of the undersigned attorney, RADIL's assay surface is prepared by the method of claim 49.

Accordingly, a rigid comparison of RADIL's methods and products with the claims of the present application has led the undersigned attorney to the opinion that at least claims 36, 46, 54 and 60 of the present application are unquestionably infringed. Applicant, therefore, requests expedited consideration under 37 C.F.R. § 1.102, and includes herein the petition fee of $130 as set forth under 37 C.F.R. § 1.17(h). If this is determined to be inaccurate, any deficiency may be charged to Deposit Account No. 19-3140.

Copies of the above-cited Web pages are provided herein.

Applicant requests that the Examiner contact the undersigned attorney by telephone if a discussion would be of benefit toward gaining rapid examination of the claims under this Petition to Make Special.

Dated: Aug 3, 2005

Respectfully submitted,

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RADIL
RESEARCH ANIMAL
DIAGNOSTIC LABORATORY
UNIVERSITY OF MISSOURI

where SCIENCE meets service

May 16, 2005

Murine Norovirus

As part of the RADIL's continuing effort to provide the highest level of diagnostic testing for research animals, the RADIL is offering MFI and PCR testing for a newly-recognized Murine norovirus.

What is known about the virus??

- **Murine norovirus (MNV) was first described by Karst et al. in 2003 (http://www.sciencemag.org/cgi/content/abstract/299/5612/1575)**

- **Experimental inoculation studies revealed that disease manifestations associated with MNV infection vary depending on the mouse strain:**
  - **Immunodeficient (RAG/STAT$^{-/-}$) mice showed high mortality with concomitant encephalitis, meningitis, vasculitis, pneumonia and hepatitis.**
  - **RAG$^{-/-}$ mice exhibited low mortality but remained persistently infected.**
  - **Immunocompetent mice seroconverted but were only transiently infected with the virus.**
  - **Mice lacking interferon αβ and interferon γ receptors were 10,000-fold more susceptible than immunocompetent mice.**

- **Testing of 2449 serum samples submitted to the RADIL during a two-week period revealed that 29.9% of samples were seropositive; thus, MNV is highly prevalent in contemporary laboratory animal facilities.**

- **Studies with MNV are ongoing at the RADIL to further investigate the diagnosis, transmission, pathogenesis and pathogenic effects of the virus.**

MNV MFI testing is available as an option for all RADIL mouse profiles. The

charge for MNV, when added to a profile, will be $5.65 per test. Individual MNV testing is available at $8.45 per sample. Confirmatory testing, if needed, is available by IFA and Western Blot.

MNV testing by PCR is available as an individual test for a cost of $55.00 or can be added to an IMPACT Profile for $25.00.

If you have questions or need additional information regarding MNV or other diagnostic testing needs please contact us at 800-669-0825 or radil@missouri.edu.

1. **Why is the RADIL switching primary serology testing from ELISA to MFI?**
   MFI offers many advantages over ELISA. Among them are: increased sensitivity and specificity, better reproducibility, faster throughput of samples, the ability to assay for up to 100 different antigens and control preparations in a single well (multiplexing), and, most importantly to you, the ability to perform ALL primary testing on only 0.2 µl of undiluted serum.

2. **What is your timetable for conversion from ELISA to MFI and what species will you be testing with MFI?**
   Mouse and rat primary testing will be performed solely by MFI beginning February 15, 2005. MFI primary testing for hamster, guinea pig, gerbil and rabbit is under development and at present will continue to be tested by ELISA.

3. **What is MFI?**
   MFI stands for Multiplex Fluorescent Immunoassay. The technology is based both on bead-based immunoassay and flow cytometry. Each purified RADIL antigen or control preparation is covalently linked to one of 100 different types of polystyrene beads, which vary slightly in the intensity of their color. If IgG antibody to a particular antigen is present, it will bind to the antigen on a specific bead and will then be detected by subsequent binding of goat anti-mouse antibody conjugated to a fluorochrome, R-phycoerythrin. The reader channels single beads through a dual laser detector which simultaneously determines both the bead type by the internal dye combination and the fluorescent intensity associated with each individual bead. The fluorescent intensity associated with each of 100 individual beads of each type are used in the determination of each MFI value.

4. **How do MFI results compare to ELISA results?**
   The RADIL has performed comparative, side-by-side testing of thousands of individual results from hundreds of samples. The overall correlation between MFI and ELISA is greater than 99.5% for both mouse and rat samples. **In general, MFI is more sensitive than ELISA and is less prone to false positive results.**

5. **How does MFI fit into RADIL's *smart SEROLOGY* package?**
   MFI is the RADIL's new state-of-the-art primary screening assay for rodent serology. The secondary confirmatory testing technique will continue to be the indirect fluorescent antibody (IFA) test. RADIL has added Western blot (WB) as the tertiary testing technique for the ultimate in sensitivity and specificity.

6. **How much <u>more</u> will MFI and the *smart SEROLOGY* package cost me?**
   The cost of your serologic testing using the new MFI technology and RADIL's ***smart SEROLOGY*** approach will not increase over traditional ELISA testing!

7. **How much serum will I need to submit for MFI testing?**
   MFI requires only 0.2 µl of undiluted serum (1.0 µl of 1:5 diluted serum) regardless of the number of tests requested. This means that survival-bled rodents can now be comprehensively tested.

   To allow for potential secondary and tertiary confirmatory testing, **we recommend that a minimum of 20 µl of undiluted (100 µl of diluted serum) be submitted for each sample**. With the advent of MFI technology, insufficient serum volumes have become a thing of the past.

8. **What are the measurement units of MFI and how will MFI results be reported?**
   The units of MFI (Multiplex Fluorescent Immunoassay) are also called MFI (median fluorescent intensity)! The reader determines this value, which can range from less than 10 to up to 32,667 by calculating the median signal value of 100 beads for each agent and control bead set. Positive MFI results will be reported as '+' with a value between 1 and 33. This numerical value represents the MFI value rounded off to the nearest 1,000. For example, a reported MFI value of '+7' means that an MFI value of between 6,500 and 7,499 was measured. **You may either see your results in this format or you may opt for the numerical value after the + sign to be omitted.**

9. **What kinds of positive serum samples were used to validate the performance of the MFI system?**
   Wherever available, dilutions of known positive serum for mice and rats were used as the "gold standard" to assure assay performance. In addition to this type of sample, we also used samples from experimentally infected rodents and clinical samples from well-characterized outbreaks to validate the performance of MFI.

10. **How will you control for non-specifically adherent serum samples using MFI?**
    We have carefully chosen five control preparations that represent a wide spectrum of proteinaceous materials and we have established statistical parameters for determining if a given serum sample binds non-specifically to one or more of these preparations. If that occurs and we also detect binding

to antigens, we will report a result of NA for that particular antigen, just as we currently do in ELISA. Non-specific binding will always occur to some extent in serologic testing. However, it has been our experience that MFI is less prone to this problem than ELISA. Of 30 mouse samples which yielded NA by ELISA and/or NF by IFA for two or more tests, 28 samples (93%) yielded valid results using the new MFI technology. **Thus, we anticipate MFI will yield a higher percentage of testable serum samples.**

11. How were the baselines for MFI calculated?

Over 600 random negative mouse samples and 275 random negative rat samples (as determined by primary ELISA and secondary/tertiary testing as required) representing over 21,000 individual data points for all the agents and controls were used to calculate baseline values for MFI. The baselines were set at the mean plus 5 standard deviation units for each agent / species combination and rounded off to the nearest 25 MFI units. For example, the mouse MHV MFI baseline was calculated to be 373 and then rounded up to 375 (n=638). Any value under 375 will be reported as negative, any value between 375 and twice that value, 750, will be reported as borderline (*) and automatically retested by IFA, while any value greater than 750 will be reported as positive (+1 to +33).

While mean positive to negative ratios of ELISA-tested samples are typically about 10:1, mean MFI positive to negative ratios are generally 50:1 and greater. This means that from a statistical standpoint, it is much easier to differentiate between the negative and positive signals on MFI versus ELISA. **Thus, MFI testing should yield fewer equivocal results than traditional ELISA**.